NATIONAL GUIDELINE CLEARINGHOUSE™ (NGC) GUIDELINE SYNTHESIS

DIAGNOSIS AND MANAGEMENT OF STABLE CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

GUIDELINES BEING COMPARED

1. **American College of Physicians (ACP)**. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2007 Nov 6;147(9):633-8. [54 references]
2. **Global Initiative for Chronic Obstructive Lung Disease (GOLD)**. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Bethesda (MD): Global Initiative for Chronic Obstructive Lung Disease (GOLD); 2008. 94 p. [435 references]
3. **Singapore Ministry of Health (SMOH)**. Chronic obstructive pulmonary disease. Singapore: Singapore Ministry of Health; 2006 Oct. 84 p. [155 references]

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AREAS OF AGREEMENT AND DIFFERENCE

A direct comparison of the American College of Physicians (ACP), the Global Initiative for Chronic Obstructive Lung Disease (GOLD), and the Singapore Ministry of Health (SMOH) recommendations for the diagnosis and management of stable COPD is provided in the tables below. Recommendations for Diagnosis and Management of Acute Exacerbations and Pulmonary Rehabilitation are addressed in separate syntheses.

Areas of Agreement

Clinical Presentation and Spirometry

There is overall agreement that the diagnosis of COPD is suspected on the basis of respiratory symptoms (e.g., dyspnea, chronic cough, sputum production), and confirmed by spirometry.

There is also overall agreement that physical examination is rarely diagnostic in COPD. GOLD and SMOH specify that physical signs of airflow obstruction are usually not present until significant lung function impairment has occurred, and their detection has a relatively low sensitivity and specificity.

Additional Investigations

The only groups to address investigations beyond spirometry are GOLD and SMOH. GOLD specifies that the additional investigations may be considered for patients diagnosed with *Stage II: Moderate COPD* and beyond.

GOLD and SMOH agree that chest x-ray is of limited value in the diagnosis of COPD, but that it is helpful to exclude alternative diagnoses and identify comorbidities. They also agree that routine CT of the chest is not recommended. GOLD notes, however, that when there is diagnostic doubt, HRCT scanning might help in the differential diagnosis. They add that if LVRS is contemplated, a chest CT scan is necessary since the distribution of emphysema is one of the most important determinants of surgical suitability.

There is further agreement that blood gas analysis should be performed in patients with FEV_1 < 50% (GOLD) or FEV_1 < 40% (SMOH), or with clinical signs suggestive of respiratory failure or right heart failure.

Differential Diagnosis

The two groups to address differential diagnosis, GOLD and SMOH, agree that the primary differential diagnosis for COPD is asthma. The groups further agree that where chronic asthma cannot be distinguished from COPD with current imaging or physiological testing, it is assumed that the two diseases co-exist and their management should be similar to that of asthma. Other potential diagnoses cited by both groups include congestive heart failure, bronchiectasis, and obliterative bronchiolitis.

Other Pharmacologic Agents

GOLD and SMOH are the only groups to address other pharmacologic agents. Both groups recommend influenza vaccination in COPD patients. GOLD also recommends the pneumococcal vaccine in COPD patients 65 years and older. SMOH states that pneumococcal vaccination may be considered in COPD patients, and if considered, usually only one dose of the vaccine is needed. A second dose is recommended for persons aged 65 or older who received their first dose when they were under 65, if 5 or more years have passed.

The groups are in agreement that the following pharmacologic agents cannot be recommended: prophylactic antibiotic therapy, mucolytics, vasodilators, nedocromil and leukotriene modifiers, and antioxidants. GOLD also recommends against the regular use of antitussives and immunoregulators. With regard to other agents, GOLD states that oral and parenteral opioids are effective for treating dyspnea in patients with advanced disease. They caution, however, that some clinical studies suggest that morphine used to control dyspnea may have serious adverse effects and its benefits may be limited to a few sensitive subjects. GOLD also addresses AAT augmentation therapy, noting that young patients with severe hereditary AAT deficiency and established emphysema may be candidates for AAT augmentation therapy.

Oxygen Therapy

There is overall agreement that administration of oxygen for 15 or more hours daily can help improve survival in patients with chronic respiratory failure. There is also overall agreement that oxygen therapy should be administered to patients with PaO_2 < 55 mm Hg. GOLD and SMOH further agree that oxygen therapy can be recommended for patients with PaO_2 between 55 mm Hg and 60 mm Hg when there is evidence of pulmonary hypertension, congestive heart failure, or polycythaemia (hematocrit > 55%).

Surgery

The two guidelines that address surgery, GOLD and SMOH, generally agree that surgery may be appropriate management of COPD in qualifying individuals, and both address bullectomy, lung transplant and LVRS as possible surgical options.

Areas of Difference

Assessing Severity of Disease

GOLD describes a four-stage system (mild, moderate, severe, and very severe) and SMOH the five-stage system previously employed by GOLD. In previous versions of its guideline, GOLD identified an early stage of COPD (*Stage 0*), in which a person has chronic symptoms of COPD but normal spirometry. They have since modified the spirometric classification to no longer include Stage 0, as there is incomplete evidence that individuals who meet the definition of "At Risk" (chronic cough and sputum production, normal spirometry) necessarily progress on to *Stage I*. The SMOH guideline, however, relies on the previous GOLD classification scheme and therefore includes the *Stage 0* category. ACP does not recommend a specific spirometric classification, but cites the schemes used by GOLD and the American Thoracic Society/European Respiratory Society.

Clinical Presentation and Spirometry

While GOLD and SMOH recommend spirometry be performed in patients with respiratory symptoms **and/or** a history of exposure to risk factors for COPD, ACP states that evidence does not support the use of spirometry to screen for airflow obstruction in asymptomatic individuals, including those who have risk factors for COPD.

Additional Investigations

The only groups to address investigations beyond spirometry are GOLD and SMOH. GOLD specifies that the additional investigations may be considered for patients diagnosed with *Stage II: Moderate COPD* and beyond.

Recommendations regarding the indications for reversibility testing differ. GOLD recommends against it, stating that neither bronchodilator nor oral glucocorticosteroid reversibility testing predicts disease progression, whether judged by decline in FEV_1, deterioration of health status, or frequency of exacerbations in patients with a clinical diagnosis of COPD and abnormal spirometry. They acknowledge, however, that in some cases (e.g., a patient with an atypical history such as asthma in childhood and regular night waking with cough or wheeze) a clinician may wish to perform a bronchodilator and/or glucocorticosteroid reversibility test and suggest a possible protocol for doing so. SMOH, on the other hand, recommends that bronchodilator reversibility testing be performed to help identify some subjects with asthma or a large asthma component to COPD and to establish a patient's best attainable lung function.

An additional investigation recommended by GOLD is measurement of AAT levels in patients of Caucasian descent who develop COPD at a young age (< 45 years) or who have a strong family history of the disease. SMOH acknowledges that severe hereditary deficiency of AAT is a well-documented host factor, but does not recommend screening for AAT deficiency.

Bronchodilator and Corticosteroid Therapy

Recommendations regarding pharmacologic therapy differ somewhat. GOLD and SMOH provide pharmacotherapy recommendations according to disease severity. The therapy then becomes cumulative as the disease progresses. A typical progression cited by both groups is introduction of short-acting bronchodilators, to which are added long-acting bronchodilators if symptoms remain uncontrolled, to which are added inhaled corticosteroids for patients with $FEV_{1\ 2}$-agonist, a long-acting inhaled anticholinergic, or an inhaled corticosteroid. They note that evidence is insufficient to recommend one monotherapy over another.

Combination Pharmacologic Therapy

With regard to combining bronchodilator therapies, GOLD and SMOH agree that combining bronchodilators with different mechanisms and durations of action may increase the degree of bronchodilation for equivalent of lesser side effects. With regard to combining an inhaled corticosteroid and a LABA, GOLD states that this is more effective than the individual components in reducing exacerbations and improving lung function and health status. SMOH recommends this combination be considered for patients in whom both its components are indicated.

While ACP does state that clinicians may consider combination inhaled therapies, they take a more reserved stance than GOLD and SMOH, noting that when to use combination therapy instead of monotherapy has not been clearly established and studies of combination therapies do not consistently demonstrate benefits of combination therapy over monotherapy.

Patient Education

GOLD and SMOH agree that patient education is beneficial as part of a COPD management program to help patients cope with their illness as well as to meet specific objectives, such as education in smoking cessation. ACP, in contrast, states that the evidence did not show any effect of disease management programs or patient education on deaths, COPD exacerbations, reduction in all-cause readmissions, hospital length of stay, visits to primary care physicians, clinically meaningful improvement in the St. George Respiratory Questionnaire health status score, patient satisfaction, self management skills, or adherence to treatment.

COMPARISON OF RECOMMENDATIONS	
DIAGNOSIS **Abbreviations** **Back to TOC**	
Clinical Presentation and Spirometry	
ACP (2007)	*Recommendation: In patients with respiratory symptoms, particularly dyspnea, spirometry should be performed to diagnose airflow obstruction. Spirometry should not be used to screen for airflow obstruction in asymptomatic individuals.* **(Grade: strong recommendation, moderate-quality evidence.)** Targeted use of spirometry for diagnosis of AO is beneficial for individuals with respiratory symptoms, particularly dyspnea. Evidence does not support the use of spirometry to screen for airflow obstruction in asymptomatic individuals, including those who have risk factors for COPD. No high quality evidence supports obtaining and providing spirometry results to improve smoking cessation, or to identify and treat asymptomatic individuals to prevent future respiratory symptoms or reduce spirometric decline in lung function.
GOLD (2008)	**Key Points**: • A clinical diagnosis of COPD should be considered in any patient who has dyspnea, chronic cough or sputum production, and/or a history of exposure to risk factors for the disease (see below). The diagnosis should be confirmed by spirometry.

Key Indicators for Considering a Diagnosis of COPD

Consider COPD, and perform spirometry, if any of these indicators are present in an individual over age 40. These indicators are not diagnostic themselves, but the presence of multiple key indicators increases the probability of a diagnosis of COPD. Spirometry is needed to establish a diagnosis of COPD.

- **Dyspnea that is**:
  - Progressive (worsens over time)
  - Usually worse with exercise
  - Persistent (present every day)
  - Described by the patient as an "increased effort to breathe," "heaviness," "air hunger," or "gasping"
- **Chronic cough**: May be intermittent and may be unproductive
- **Chronic sputum production**: Any pattern of chronic sputum production may indicate COPD
- **History of exposure to risk factors**, especially:
  - Tobacco smoke
  - Occupational dusts and chemicals
  - Smoke from home cooking and heating fuels

Note: Refer to the original guideline document for additional discussion of the above symptoms.

Medical History

A detailed medical history of a new patient known or thought to have COPD should assess:

- *Patient's exposure to risk factors*, such as smoking and occupational or environmental exposures
- *Past medical history*, including asthma, allergy, sinusitis or nasal polyps, respiratory infections in childhood, and other respiratory diseases
- *Family history of COPD or other chronic respiratory disease*
- *Pattern of symptom development*: COPD typically develops in adult life and most patients are conscious of increased breathlessness, more frequent "winter colds," and some social restriction for a number of years before seeking medical help
- *History of exacerbations or previous hospitalizations for respiratory disorder*: Patients may be aware of periodic worsening of symptoms even if these episodes have not been identified as exacerbations of COPD
- *Presence of comorbidities*, such as heart disease, malignancies, osteoporosis, and musculoskeletal disorders, which may also contribute to restriction of activity
- *Appropriateness of current medical treatments*: For

example, beta-blockers commonly prescribed for heart disease are usually contraindicated in COPD
- *Impact of disease on patient's life*, including limitation of activity; missed work and economic impact; effect on family routines; and feelings of depression or anxiety
- *Social and family support available to the patient*
- *Possibilities for reducing risk factors*, especially smoking cessation

Physical Examination

Though an important part of patient care, a physical examination is rarely diagnostic in COPD. Physical signs of airflow limitation are usually not present until significant impairment of lung function has occurred, and their detection has a relatively low sensitivity and specificity. A number of physical signs may be present in COPD, but their absence does not exclude the diagnosis.

Key Points:

- For the diagnosis and assessment of COPD, spirometry is the gold standard as it is the most reproducible, standardized, and objective way of measuring airflow limitation. The presence of a postbronchodilator $FEV_1/FVC < 0.70$ and $FEV_1 < 80\%$ predicted confirms the presence of airflow limitation that is not fully reversible.
- Health care workers involved in the diagnosis and management of COPD patients should have access to spirometry.

Measurement of Airflow Limitation (Spirometry)

Spirometry should be undertaken in all patients who may have COPD. It is needed to make a confident diagnosis of COPD and to exclude other diagnoses that may present with similar symptoms. Although spirometry does not fully capture the impact of COPD on a patient's health, it remains the gold standard for diagnosing the disease and monitoring its progression. It is the best standardized, most reproducible, and most objective measurement of airflow limitation available. Good quality spirometric measurement is possible and all health care workers who care for COPD patients should have access to spirometry. Figure 5.1-4 in the original guideline document summarizes some of the factors needed to achieve accurate test results.

Spirometry should measure the volume of air forcibly exhaled from the point of maximal inspiration (forced vital capacity, FVC) and the volume of air exhaled during the first second of this

	maneuver (forced expiratory volume in one second, FEV_1), and the ratio of these two measurements (FEV_1/FVC) should be calculated. Spirometry measurements are evaluated by comparison with reference values based on age, height, sex, and race.
SMOH (2006)	**<u>Clinical Assessment</u>** **D** - A diagnosis of COPD should be considered in any patient more than 35 years old, who has chronic cough, sputum production, or dyspnoea, and/or a history of exposure to risk factors for the disease (see Table 4 in the original guideline document). **(Grade D, Level 4)** **Physical Examination** Physical examination is rarely diagnostic in COPD. Physical signs of airflow obstruction, e.g., hyperinflation, are rarely present until significant lung function impairment has occurred. Hence their detection has a low sensitivity and specificity. Physical signs of airflow obstruction that that may be present are: • Hyperinflated chest • Purse lip breathing • Use of accessory muscle • Paradoxical movements of lower ribs • Reduced crico-sternal distance • Reduced cardiac dullness • Wheeze or quiet breath sounds Loss of muscle mass and peripheral muscle weakness are present in advanced disease. **<u>Lung Function Tests</u>** **Spirometry** **D** - Spirometry is useful for the definitive diagnosis of COPD and for the staging of disease severity, and should be performed in individuals with symptoms suggestive of COPD. **(Grade D, Level 4)** The primary benefit of spirometry is to identify COPD patients who may benefit from pharmacologic treatment in order to improve symptoms and exacerbations.
Additional Investigations	
ACP	No recommendations offered.

(2007)	
GOLD (2008)	**Additional Investigations** For patients diagnosed with *Stage II: Moderate COPD* and beyond, the following additional investigations may be considered: ***Bronchodilator reversibility testing***. Despite earlier hopes, neither bronchodilator nor oral glucocorticosteroid reversibility testing predicts disease progression, whether judged by decline in FEV_1, deterioration of health status, or frequency of exacerbations in patients with a clinical diagnosis of COPD and abnormal spirometry. Small changes in FEV_1 (e.g., < 400 mL) after administration of a bronchodilator do not reliably predict the patient's response to treatment (e.g., change in exercise capacity). Minor variations in initial airway caliber can lead to different classification of reversibility status depending on the day of testing, and the lower the pre-bronchodilator FEV_1, the greater the chance of a patient being classified as reversible even when the 200 mL volume criterion is included. In some cases (e.g., a patient with an atypical history such as asthma in childhood and regular night waking with cough or wheeze) a clinician may wish to perform a bronchodilator and/or glucocorticosteroid reversibility test and a possible protocol is suggested in Figure 5.1-6 of the original guideline document. ***Chest X-ray***. An abnormal chest x-ray is seldom diagnostic in COPD unless obvious bullous disease is present, but it is valuable in excluding alternative diagnoses and establishing the presence of significant comorbidities such as cardiac failure. Radiological changes associated with COPD include signs of hyperinflation (flattened diaphragm on the lateral chest film, and an increase in the volume of the retrosternal air space), hyperlucency of the lungs, and rapid tapering of the vascular markings. CT of the chest is not routinely recommended. However, when there is doubt about the diagnosis of COPD, HRCT scanning might help in the differential diagnosis. In addition, if a surgical procedure such as lung volume reduction is contemplated, a chest CT scan is necessary since the distribution of emphysema is one of the most important determinants of surgical suitability. ***Arterial blood gas measurement***. In advanced COPD, measurement of arterial blood gases while the patient is breathing air is important. This test should be performed in stable patients with FEV_1 < 50% predicted or with clinical signs suggestive of respiratory failure or right heart failure. Several considerations are important to ensure accurate test results. The inspired oxygen concentration (FiO_2 — normally 21% at sea level) should be noted, a particularly important point if patient is using an O_2-driven nebulizer. Changes in arterial blood gas tensions take time to occur, especially in severe

	disease. Thus, 20 to 30 minutes should pass before rechecking the gas tensions when the FiO_2 has been changed (e.g., during an assessment for domiciliary oxygen therapy). Adequate pressure must be applied at the arterial puncture site for at least one minute, as failure to do so can lead to painful bruising. *AAT deficiency screening*. In patients of Caucasian descent who develop COPD at a young age (< 45 years) or who have a strong family history of the disease, it may be valuable to identify coexisting AAT deficiency. This could lead to family screening or appropriate counseling. A serum concentration of AAT below 15 to 20% of the normal value is highly suggestive of homozygous AAT deficiency.
SMOH (2006)	**Evaluation** **D** - It is recommended that bronchodilator reversibility testing be performed to help identify some subjects with asthma or a large asthma component to COPD and to establish a patient's best attainable lung function **(Grade D, Level 4)** **D** - Arterial blood gases should be performed in patients with FEV_1 < 40% predicted or with clinical signs suggestive of respiratory failure or right heart failure. **(Grade D, Level 4)** **D** - A chest X-ray is seldom diagnostic in COPD but it is valuable in excluding alternative diagnoses and should be performed to look for abnormalities that may suggest other conditions. Computed tomography of the chest is not routinely recommended. **(Grade D, Level 4)**
Differential Diagnosis	
ACP (2007)	No recommendations offered.
GOLD (2008)	**Differential Diagnosis** In some patients with chronic asthma, a clear distinction from COPD is not possible using current imaging and physiological testing techniques and it is assumed that asthma and COPD coexist in these patients. In these cases, current management is similar to that of asthma. Other potential diagnoses are usually easier to distinguish from COPD (see below). **Differential Diagnosis of COPD** COPD • Onset in mid-life

- Symptoms slowly progressive
- Long history of tobacco smoking
- Dyspnea during exercise
- Largely irreversible airflow limitation

Asthma

- Onset early in life (often childhood)
- Symptoms vary from day to day
- Symptoms at night/early morning
- Allergy, rhinitis, and/or eczema also present
- Family history of asthma
- Largely reversible airflow limitation

Congestive Heart Failure

- Fine basilar crackles on auscultation
- Chest x-ray shows dilated heart, pulmonary edema
- Pulmonary function tests indicate volume restriction, not airflow limitation

Bronchiectasis

- Large volumes of purulent sputum
- Commonly associated with bacterial infection
- Coarse crackles/clubbing on auscultation
- Chest x-ray/computed tomography shows bronchial dilation, bronchial wall thickening

Tuberculosis

- Onset all ages
- Chest x-ray shows lung infiltrate
- Microbiological confirmation
- High local prevalence of tuberculosis

Obliterative Bronchiolitis

- Onset in younger age, nonsmokers
- May have history of rheumatoid arthritis or fume exposure
- Computed tomography on expiration shows hypodense areas

Diffuse Panbronchiolitis

- Most patients are male and nonsmokers
- Almost all have chronic sinusitis
- Chest x-ray and high resolution computed tomography (HRCT) show diffuse small centrilobular nodular opacities and hyperinflation

	Note: *These features tend to be characteristic of the respective diseases, but do not occur in every case. For example, a person who has never smoked may develop COPD (especially in the developing world, where other risk factors may be more important than cigarette smoking); asthma may develop in adult and even elderly patients.*
SMOH (2006)	**Differential Diagnosis** A major differential diagnosis of COPD is bronchial asthma. These two conditions are frequently distinguishable on the basis of history and examination in untreated patients presenting for the first time. Table 1 in the original guideline document shows the features that help to differentiate between COPD and Asthma. **D** - Where diagnostic doubt remains, or both COPD and asthma are present, the following findings will help identify asthma: • A large response (FEV_1 greater than 400 mL) to bronchodilators • A large response (FEV_1 greater than 400 mL) to 30 mg oral prednisolone daily for 2 weeks • Serial peak flow measurements showing 20% or greater diurnal or day-to-day variability **(Grade D, Level 4)** The definition of COPD requires confirmation of persistent airflow obstruction after administration of a bronchodilator. Bronchoreversibility, however, cannot serve as an absolute criterion for separating asthma from COPD. On the other hand, documentation of complete reversibility is useful in excluding COPD, and a documentation of bronchoreversibility of a rise of FEV_1 > 400 mL has been suggested to indicate such a reversibility. Similarly, a variation of 20% or greater diurnal or day-to-day variability is the level for documenting complete bronchoreversibility. **D** - Where chronic asthma cannot be distinguished from COPD with the current imaging or lung function testing, it is assumed that the two diseases co-exist and their management should be similar to that of asthma. **(Grade D, Level 4)** **D** - COPD should be differentiated from congestive heart failure, bronchiectasis, and obliterative bronchiolitis. **(Grade D, Level 4)** Congestive heart failure, bronchiectasis, and obliterative bronchiolitis may present with similar symptoms and signs as COPD. These conditions may mimic COPD or may co-exist in a patient with COPD. See Table 2 in the original guideline document.

Assessing Severity of Disease	
ACP (2007)	See Table 2 "Spirometric Classifications of COPD" in the original guideline document for the classification schemes used by GOLD and the American Thoracic Society/European Respiratory Society.
GOLD (2008)	**Assessment of COPD Severity** Assessment of COPD severity is based on the patient's level of symptoms, the severity of the spirometric abnormality (Figure 1-2 in the original guideline document), and the presence of complications such as respiratory failure, right heart failure, weight loss, and arterial hypoxemia. **Spirometric Classification of Severity** For educational reasons, a simple spirometric classification of disease severity into four stages is recommended (see below). Spirometry is essential for diagnosis and provides a useful description of the severity of pathological changes in COPD. Specific spirometric cut-points (e.g., post-bronchodilator FEV_1/FVC ratio < 0.70 or FEV1 < 80, 50, or 30% predicted) are used for purposes of simplicity: these cut-points have not been clinically validated. **Stage I [Mild COPD]** • $FEV_1/FVC < 0.70$ • $FEV_1 \geq 80\%$ predicted **Stage II [Moderate COPD]** • $FEV_1/FVC < 0.70$ • $50\% \leq FEV_1 < 80\%$ predicted **Stage III [Severe COPD]** • $FEV_1/FVC < 0.70$ • $30\% \leq FEV_1 < 50\%$ predicted **Stage IV [Very Severe COPD]** • $FEV_1/FVC < 0.70$ • $FEV_1 < 30\%$ predicted or FEV1 < 50% predicted plus chronic respiratory failure
SMOH (2006)	**Classification of Severity**

Spirometry

D - A classification of disease severity into 5 stages based on spirometry cut points is recommended. **(Grade D, Level 4)**

The FEV_1 and FEV_1/FVC cut-points used by GOLD for classifying the severity of COPD into 5 stages are shown below. These cut points are used for the purposes of educational simplicity: they have not been clinically validated.

Stage 0 [At Risk]

- Normal spirometry
- Chronic symptoms (cough, sputum production)

Stage I [Mild COPD]

- FEV_1/FVC < 70%
- $FEV_1 \geq$80% predicted
- With or without chronic symptoms (cough, sputum production)

Stage II [Moderate COPD]

- FEV_1/FVC < 70%
- 50% $\leq$ FEV_1 < 80% predicted
- With or without chronic symptoms (cough, sputum production)

Stage III [Moderate COPD]

- FEV_1/FVC < 70%
- 30% $\leq$ FEV_1 < 50% predicted
- With or without chronic symptoms (cough, sputum production)

Stage IV [Very Severe COPD]

- FEV_1/FVC < 70%

FEV_1 < 30% predicted or FEV1 < 50% predicted plus chronic respiratory failure

Assessment of Severity

Assessment of severity is based on the patient's level of symptoms, the severity of the spirometric abnormality, and the presence of complications such as cor pulmonale, respiratory failure and right heart failure.

Physical signs of cor pulmonale to look for are:

	• Central cyanosis • Raised jugular venous pressure • Left parasternal heave • Loud P2 and a loud ejection click • Pansystolic murmur or tricuspid regurgitation • Hepatomegaly • Peripheral oedema Progressive impairment of consciousness, the presence of a bounding pulse, flapping tremor and papilloedema indicate carbon dioxide retention and impending respiratory failure.
PHARMACOLOGIC INTERVENTIONS **Abbreviations** **Back to TOC**	
Bronchodilator and Corticosteroid Therapy	
ACP (2007)	*Recommendation: Treatment for stable COPD should be reserved for patients who have respiratory symptoms and FEV1 less than 60% predicted as documented by spirometry.* **(Grade: strong recommendation, moderate-quality evidence.)** Evidence shows that individuals who will benefit the most from therapy are those who have respiratory symptoms and clinically significant AO (FEV_1 < 60% predicted). No evidence supports treating asymptomatic patients because treatment does not improve outcomes. The evidence does not support periodic spirometry after initiation of therapy to monitor ongoing disease status or to modify therapy. This recommendation does not address the occasional use of bronchodilators for acute symptomatic relief. *Recommendation: Clinicians should prescribe 1 of the following maintenance monotherapies for symptomatic patients with COPD and FEV_1 less than 60% predicted: long-acting inhaled $beta_2$-agonists, long-acting inhaled anticholinergics, or inhaled corticosteroids.* **(Grade: strong recommendation, high-quality evidence.)** Monotherapy with a long-acting inhaled $beta_2$-agonist, a long-acting inhaled anticholinergic, or an inhaled corticosteroid is beneficial in reducing exacerbations. Inhaled corticosteroids and long-acting inhaled bronchodilators have similar effectiveness but differ in adverse effects, reductions in deaths, and hospitalizations. The review did not systematically evaluate all other outcomes. Evidence is insufficient to recommend one monotherapy over another. *Recommendation: Clinicians may consider combination inhaled therapies for symptomatic patients with COPD and FEV_1 less than 60% predicted.* ***(Grade: weak recommendation, moderate-***

	quality evidence.) *When to use combination therapy instead of monotherapy has not been clearly established. In the TORCH trial, combination therapy with long-acting beta$_2$-agonists and corticosteroids reduced exacerbations more than did monotherapy. Although deaths with combination therapy decreased in the trial compared with monotherapy, the reduction did not reach the predetermined level of statistical significance. In a recent randomized trial, addition of salmeterol—fluticasone to tiotropium therapy did not statistically influence rates of COPD exacerbation but did improve lung function, quality of life, and hospitalization rates in patients with moderate to severe COPD. However, studies of combination therapies do not consistently demonstrate benefits of combination therapy over monotherapy.*
GOLD (2008)	**Key Points**: • None of the existing medications for COPD have been shown to modify the long-term decline in lung function that is the hallmark of this disease **(Evidence A)**. Therefore, pharmacotherapy for COPD is used to decrease symptoms and/or complications. • Bronchodilator medications are central to the symptomatic management of COPD **(Evidence A)**. They are given on an as-needed basis or on a regular basis to prevent or reduce symptoms and exacerbations. • The principal bronchodilator treatments are beta$_2$-agonists, anticholinergics, and methylxanthines used singly or in combination **(Evidence A)**. • Regular treatment with long-acting bronchodilators is more effective and convenient than treatment with short-acting bronchodilators **(Evidence A)**. • The addition of regular treatment with inhaled glucocorticosteroids to bronchodilator treatment is appropriate for symptomatic COPD patients with an FEV_1 < 50% predicted (*Stage III: Severe COPD and Stage IV*: Very Severe COPD) and repeated exacerbations **(Evidence A)**. • Chronic treatment with systemic glucocorticosteroids should be avoided because of an unfavorable benefit-to-risk ratio **(Evidence A)**. The classes of medications commonly used in treating COPD are shown in Figure 5.3-4 of the original guideline document. **Overview of the Medications** Pharmacologic therapy is used to prevent and control symptoms, reduce the frequency and severity of exacerbations, improve health status, and improve exercise tolerance. None of the existing medications for COPD has been shown to modify the long-term

decline in lung function that is the hallmark of this disease. However, this should not preclude efforts to use medications to control symptoms. Since COPD is usually progressive, recommendations for the pharmacological treatment of COPD reflect the following general principles:

- Treatment tends to be cumulative with more medications being required as the disease state worsens.
- Regular treatment needs to be maintained at the same level for long periods of time unless significant side effects occur or the disease worsens.

Individuals differ in their response to treatment and in the side effects they report during therapy. Careful monitoring is needed over an appropriate period to ensure that the specific aim of introducing a therapy has been met without an unacceptable cost to the patient. The effect of therapy in COPD may occur sooner after treatment with bronchodilators and inhaled glucocorticosteroids than previously thought, although at present, there is no effective way to predict whether or not treatment will reduce exacerbations.

Bronchodilators

Methylxanthines

Theophylline is effective in COPD but, due to its potential toxicity, inhaled bronchodilators are preferred when available. Low dose theophylline reduces exacerbations in patients with COPD but does not increase post-bronchodilator lung function **(Evidence B)**. Higher doses of theophylline are effective bronchodilators in COPD but, due to the potential for toxicity, inhaled bronchodilators are preferred.

Combination bronchodilator therapy. Although monotherapy with long-acting $beta_2$-agonists appears to be safe, combining bronchodilators with different mechanisms and durations of action may increase the degree of bronchodilation for equivalent or lesser side effects. For example, a combination of a short-acting $beta_2$-agonist and an anticholinergic produces greater and more sustained improvements in FEV_1 than either drug alone and does not produce evidence of tachyphylaxis over 90 days of treatment **(Evidence A)**.

The combination of a $beta_2$-agonist, an anticholinergic and/or theophylline may produce additional improvements in lung function and health status. Increasing the number of drugs usually increases costs, and an equivalent benefit may occur by increasing the dose of one bronchodilator when side effects are not a limiting factor. Detailed assessments of this approach have not been carried out.

Glucocorticosteroids

The effects of oral and inhaled glucocorticosteroids in COPD are much less dramatic than in asthma, and their role in the management of stable COPD is limited to specific indications. The use of glucocorticosteroids for the treatment of acute exacerbations is described in Component 4: Manage Exacerbations of the original guideline document.

Inhaled glucocorticoids. Regular treatment with inhaled glucocorticosteroids does not modify the long-term decline of FEV_1 in patients with COPD. However, regular treatment with inhaled glucocorticosteroids has been shown to reduce the frequency of exacerbations and thus improve health status for symptomatic COPD patients with an FEV_1 < 50% predicted (*Stage III: Severe COPD and Stage IV: Very Severe COPD*) and repeated exacerbations (for example, 3 in the last three years) **(Evidence A)** and withdrawal from treatment with inhaled glucocorticosteroids can lead to exacerbations in some patients. Treatment with inhaled glucocorticosteroids increases the likelihood of pneumonia and does not reduce overall mortality.

Combination inhaled glucocorticosteroid/bronchodilator therapy: An inhaled glucocorticosteroid combined with a long-acting $beta_2$-agonist is more effective than the individual components in reducing exacerbations and improving lung function and health status **(Evidence A)**.

Oral glucocorticoids: short-term. Many existing COPD guidelines recommend the use of a short course (two weeks) of oral glucocorticosteroids to identify COPD patients who might benefit from long-term treatment with oral or inhaled glucocorticosteroids.

There is mounting evidence, however, that a short course of oral glucocorticosteroids is a poor predictor of the long-term response to inhaled glucocorticosteroids in COPD. For this reason, there appears to be insufficient evidence to recommend a therapeutic trial with oral glucocorticosteroids in patients with *Stage II: Moderate COPD*, *Stage III: Severe COPD*, or *Stage IV: Very Severe COPD* and poor response to an inhaled bronchodilator.

Oral glucocorticoids: long-term. Based on the lack of evidence of benefit, and the large body of evidence on side effects, long-term treatment with oral glucocorticosteroids is not recommended in COPD **(Evidence A)**.

Pharmacologic Therapy by Disease Severity

Figure 5.3-7 in the original guideline document provides a summary of recommended treatment at each stage of COPD.

SMOH (2006)	**Goals of Pharmacotherapy in COPD** • Relieve, reduce and abolish symptoms • Increase exercise capacity • Reduce frequency and severity of acute exacerbations • Improve health related quality of life These goals should be achieved with minimum side-effects from the medications. There is currently no evidence that any pharmacotherapy influences lung function decline or mortality in COPD. Evidence from large-scale studies regarding the effect of pharmacotherapy on these outcome measures is anticipated in the near future. **Principles of Therapy** • Treatment needs to be maintained long-term. • Treatment is according to stage of severity, with step-wise increase usually required, as COPD is a progressive disease. Inhaled therapy via metered dose or dry powder inhalers is preferred. The use of a large-volume spacer is advised for patients who have difficulty mastering the metered-dose inhaler technique. **Pharmacotherapy for Stable COPD** **Short-acting Inhaled Bronchodilators** **A** - Inhaled short-acting bronchodilators are recommended as first-line therapy in all stages of COPD to relieve symptoms and improve exercise capacity. **(Grade A, Level 1+)** **Long-acting Inhaled Bronchodilators** **A** - Regular treatment with one or both classes of the inhaled long-acting bronchodilators should be considered for patients with moderate to very severe COPD with frequent exacerbations. **(Grade A, Level 1+)** **D** - Inhaled long-acting bronchodilators may be added to the treatment regimen when symptoms are not controlled with short-acting inhaled bronchodilators alone. **(Grade D, Level 4)** LABAs should be reserved for COPD patients who report definite improvement (in terms of better exercise capacity or reduced symptoms) whilst on this therapy.

	Combined Use of a Short or Long-anticholinergic and LABA Combining bronchodilators with different mechanisms and durations of actions may increase the degree of bronchodilation for equivalent or fewer side-effects. Previous studies in patients with moderate to severe stable COPD demonstrated that combination of ipratropium with either formoterol or salmeterol is more effective than a combination of the anti-cholinergic with SABAs, and shows additive effects in improving lung function. RCTs have pointed favorably in the direction of combination of tiotropium with a LABA. Findings suggest that since tiotropium ensures prolonged bronchodilation, whereas formoterol adds fast onset and a greater peak effect, the two drugs appear complementary. **Theophylline** **D** - Theophylline may be a useful addition where symptom control is still not achieved with existing inhaled bronchodilator therapy. Theophylline may be of value for patients who are non-adherent to or unable to use inhaled therapy. **(Grade D, Level 4)** **Inhaled Corticosteroids** **A** - Inhaled corticosteroids as long-term maintenance therapy are recommended for patients with FEV_1 < 50% predicted who experience frequent exacerbations. **(Grade A, Level 1+)** *Oral Corticosteroids* **A** - Long-term oral corticosteroids are not recommended in stable COPD. **(Grade A, Level 1+)** Although a short course of high dose oral corticosteroid (prednisolone 30 mg/day) can improve lung function in some COPD patients, long term use of lower doses (prednisolone at < 10 to 15 mg/day) does not prevent worsening of the condition and is associated with increased risk of adverse effects such as diabetes and osteoporosis. **Combination ICS + LABA** **D** - Combination inhaled corticosteroids and LABAs should be considered for patients in whom both its components are indicated. **(Grade D, Level 4)**
Other Pharmacologic Agents	
ACP (2007)	No recommendations offered.

GOLD (2008)	*Vaccines*. Influenza vaccines can reduce serious illness and death in COPD patients by about 50% **(Evidence A)**. Vaccines containing killed or live, inactivated viruses are recommended as they are more effective in elderly patients with COPD. The strains are adjusted each year for appropriate effectiveness and should be given once each year. Pneumococcal polysaccharide vaccine is recommended for COPD patients 65 years and older. In addition, this vaccine has been shown to reduce the incidence of community-acquired pneumonia in COPD patients younger than age 65 with an FEV_1 < 40% predicted **(Evidence B)**. *AAT augmentation therapy*. Young patients with severe hereditary AAT deficiency and established emphysema may be candidates for AAT augmentation therapy. However, this therapy is very expensive, is not available in most countries, and is not recommended for patients with COPD that is unrelated to AAT deficiency **(Evidence C)**. *Antibiotics*. Prophylactic, continuous use of antibiotics has been shown to have no effect on the frequency of exacerbations in COPD and a study that examined the efficacy of winter chemoprophylaxis over a period of 5 years, concluded that there was no benefit. There is no current evidence that the use of antibiotics, other than for treating infectious exacerbations of COPD and other bacterial infections, is helpful **(Evidence A)**. *Mucolytic (mucokinetic, mucoregulator) Agents*: (ambroxol, erdosteine, carbocysteine, iodinated glycerol). The regular use of mucolytics in COPD has been evaluated in a number of long-term studies with controversial results. Although a few patients with viscous sputum may benefit from mucolytics, the overall benefits seem to be very small, and the widespread use of these agents cannot be recommended at present **(Evidence D)**. *Antioxidant agents*. Antioxidants, in particular N-acetylcysteine, have been reported in small studies to reduce the frequency of exacerbations, leading to speculations that these medications could have a role in the treatment of patients with recurrent exacerbations **(Evidence B)**. However, a large randomized controlled trial found no effect of N-acetylcysteine on the frequency of exacerbations, except in patients not treated with inhaled glucocorticosteroids. *Immunoregulators (immunostimulators, immunomodulators)*. Studies using an immunoregulator in COPD show a decrease in the severity and frequency of exacerbations. However, additional studies to examine the long-term effects of this therapy are required before its regular use can be recommended. *Antitussives*. Cough, although sometimes a troublesome symptom in COPD, has a significant protective role. Thus, the regular use of

	antitussives is not recommended in stable COPD **(Evidence D)**. *Vasodilators*. The belief that pulmonary hypertension in COPD is associated with a poorer prognosis has provoked many attempts to reduce right ventricular afterload, increase cardiac output, and improve oxygen delivery and tissue oxygenation. Many agents have been evaluated, including inhaled nitric oxide, but the results have been uniformly disappointing. In patients with COPD, in whom hypoxemia is caused primarily by ventilation-perfusion mismatching rather than by increased intrapulmonary shunt (as in noncardiogenic pulmonary edema), inhaled nitric oxide can worsen gas exchange because of altered hypoxic regulation of ventilation-perfusion balance. Therefore, based on the available evidence, nitric oxide is contraindicated in stable COPD. *Narcotics (morphine)*. Oral and parenteral opioids are effective for treating dyspnea in COPD patients with advanced disease. There are insufficient data to conclude whether nebulized opioids are effective. However, some clinical studies suggest that morphine used to control dyspnea may have serious adverse effects and its benefits may be limited to a few sensitive subjects. *Others*. Nedocromil and leukotriene modifiers have not been adequately tested in COPD patients and cannot be recommended. There was no evidence of benefit—and some evidence of harm (malignancy and pneumonia)—from an anti-TNF-alpha antibody (infliximab) tested in moderate to severe COPD. There is no evidence of the effectiveness of herbal medicines for treating COPD and other alternative healing methods have not been adequately tested.
SMOH (2006)	**Vaccines** **C** - Annual influenza vaccination should be offered to the elderly (65 years and above) in all stages of COPD. **(Grade C, Level 2++)** **D** - Pneumococcal vaccination may be considered in COPD patients. **(Grade D, Level 4)** **D** - If considering pneumococcal vaccination for a COPD patient, usually only one dose of the vaccine is needed. A second dose is recommended for persons aged 65 or older who received their first dose when they were under 65, if 5 or more years have passed since that dose. **(Grade D, Level 4)** **Others** There is no evidence to date to support the benefit of the routine use of maintenance antibiotic therapy, mucolytics/anti-oxidants,

	respiratory stimulants, vasodilators, nedocromil sodium or leukotriene modifiers in stable COPD.
NON-PHARMACOLOGIC INTERVENTIONS **Abbreviations** **Back to TOC**	
Oxygen Therapy	
ACP (2007)	*Recommendation: Clinicians should prescribe oxygen therapy in patients with COPD and resting hypoxemia ($PaO_2 \leq 55$ mm Hg)*. **(Grade: strong recommendation, moderate quality evidence.)** Use of supplemental oxygen for 15 or more hours daily can help improve survival in patients with severe AO (FEV_1 < 30% predicted) and resting hypoxemia.
GOLD (2008)	**Key Points**: • The long-term administration of oxygen (> 15 hours per day) to patients with chronic respiratory failure has been shown to increase survival **(Evidence A)**. **Oxygen Therapy** Oxygen therapy, one of the principal nonpharmacologic treatments for patients with *Stage IV: Very Severe COPD*, can be administered in three ways: long-term continuous therapy, during exercise, and to relieve acute dyspnea. The primary goal of oxygen therapy is to increase the baseline PaO_2 to at least 8.0 kPa (60 mm Hg) at sea level and rest, and/or produce an SaO_2 at least 90%, which will preserve vital organ function by ensuring adequate delivery of oxygen. LTOT is generally introduced in Stage IV: Very Severe COPD for patients who have: • PaO_2 at or below 7.3 kPa (55 mm Hg) or SaO_2 at or below 88%, with or without hypercapnia **(Evidence B)** • PaO_2 between 7.3 kPa (55 mm Hg) and 8.0 kPa (60 mm Hg), or SaO_2 of 88%, if there is evidence of pulmonary hypertension, peripheral edema suggesting congestive cardiac failure, or polycythemia (hematocrit > 55%) **(Evidence D)** A decision about the use of LTOT should be based on the waking PaO_2 values. The prescription should always include the source of supplemental oxygen (gas or liquid), method of delivery, duration of use, and the flow rate at rest, during exercise, and during sleep. A detailed review of the uses of oxygen in COPD, together with possible assessment algorithms and information about methods of

	delivery, is available from http://www.thoracic.org. A number of physiological studies have shown that delivering oxygen during exercise can increase the duration of endurance exercise and/or reduce the intensity of end-exercise breathlessness **(Evidence A)**. Oxygen therapy reduces the oxygen cost of breathing and minute ventilation, a mechanism that although still disputed helps to minimize the sensation of dyspnea. This has led to the use of short burst therapy to control severe dyspnea such as occurs after climbing stairs. However, there is no benefit from using short burst oxygen for symptomatic relief before or after exercise **(Evidence B)**. *Oxygen use in air travel*. Although air travel is safe for most patients with chronic respiratory failure who are on long-term oxygen therapy, patients should be instructed to increase the flow by 1 to 2 L/min during the flight. Ideally, patients who fly should be able to maintain an in-flight PaO_2 of at least 6.7 kPa (50 mm Hg). Studies indicate that this can be achieved in those with moderate to severe hypoxemia at sea level by supplementary oxygen at 3 L/min by nasal cannulae or 31% by Venturi facemask. Those with a resting PaO_2 at sea level of > 9.3 kPa (70 mm Hg) are likely to be safe to fly without supplementary oxygen, although it is important to emphasize that a resting PaO_2 > 9.3 kPa (70 mm Hg) at sea level does not exclude the development of severe hypoxemia when travelling by air **(Evidence C)**.
SMOH (2006)	**Oxygen Therapy in COPD** **A** - Patients with very severe COPD and chronic respiratory failure should be assessed for the need for LTOT. **(Grade A, Level 1+)** **A** - Indications for LTOT (at least 15 hours/day) in patients with COPD should be based on the following indices obtained in stable state: • Without pulmonary hypertension (Cor Pulmonale), congestive heart failure, polycythaemia (Hct > 55%): 1. $PaO_2 \leq$ 55 mmHg on Room Air OR 2. $SaO_2 \leq$ 89% on Room Air • With pulmonary hypertension (Cor Pulmonale), congestive heart failure, polycythaemia (Hct > 55%):

	1. PaO_2 between 55 mmHg — 60 mmHg on Room Air OR 2. $SaO_2 \leq$ 89% on Room Air **(Grade A, Level 1+)** **D** - Oxygen concentrator is the preferred mode of delivery of oxygen. It is the most convenient and economical method of providing LTOT. **(Grade D, Level 3)** **D** - Very severe COPD patients with hypercapnic respiratory failure requiring LTOT should have the oxygen flow rate titrated cautiously to maintain a $SaO_2 \geq$ 90%. **(Grade D, Level 4)**
Lifestyle Modification	
ACP (2007)	No recommendations offered.
GOLD (2008)	**Key Points**: • Reduction of total personal exposure to tobacco smoke, occupational dusts and chemicals, and indoor and outdoor air pollutants are important goals to prevent the onset and progression of COPD. • Smoking cessation is the single most effective–and cost effective–intervention in most people to reduce the risk of developing COPD and stop its progression **(Evidence A)**. • Comprehensive tobacco control policies and programs with clear, consistent, and repeated nonsmoking messages should be delivered through every feasible channel. • Efforts to reduce smoking through public health initiatives should also focus on passive smoking to minimize risks for nonsmokers. • Many occupationally induced respiratory disorders can be reduced or controlled through a variety of strategies aimed at reducing the burden of inhaled particles and gases. • Reducing the risk from indoor and outdoor air pollution is feasible and requires a combination of public policy and protective steps taken by individual patients. **Smoking Cessation** The Public Health Service Guidelines recommend a five-step program for intervention (Figure 5.2-3 in the original guideline document), which provides a strategic framework helpful to health care providers interested in helping their patients stop smoking. The guidelines emphasize that tobacco dependence is a chronic disease (Figure 5.2-4 in the original guideline document) and urge clinicians to recognize

	that relapse is common and reflects the chronic nature of dependence and addiction, not failure on the part of the clinician or the patient. Most individuals go through several stages before they stop smoking (Figure 5.2-5 in the original guideline document). It is often helpful for the clinician to assess a patient's readiness to quit in order to determine the most effective course of action at that time. The clinician should initiate treatment if the patient is ready to quit. For a patient not ready to make a quit attempt, the clinician should provide a brief intervention designed to promote the motivation to quit. *Counseling*. Counseling delivered by physicians and other health professionals significantly increases quit rates over self-initiated strategies. Even a brief (3-minute) period of counseling to urge a smoker to quit results in smoking cessation rates of 5 to 10%. At the very least, this should be done for every smoker at every health care provider visit. Education in how to offer optimal smoking cessation advice and support should be a mandatory element of curricula for health professionals. *Pharmacotherapy*. Numerous effective pharmacotherapies for smoking cessation now exist, and pharmacotherapy is recommended when counseling is not sufficient to help patients quit smoking. Special consideration should be given before using pharmacotherapy in selected populations: people with medical contraindications, light smokers (fewer than 10 cigarettes/day), and pregnant and adolescent smokers. (Refer to the original guideline for specific recommendations regarding pharmacotherapy.)
SMOH (2006)	**Nutrition in COPD** **D** - All patients with COPD should undergo simple nutrition screening. **(Grade D, Level 4)** **GPP** - Nutritional intervention should be considered in all COPD patients with BMI < 18.5 kg/m^2 or significant involuntary weight loss (> 10% during the last 6 months or > 5% in the past month). **(GPP)** **Smoking Cessation** **A** - Smoking cessation should be emphasized as an essential first step in management of COPD patients. **(Grade A, Level 1++)** **GPP** - Clinicians should play a prominent role in promoting attempts

	to stop smoking in their patients. **(GPP)** **A** - All smokers, including those who may be at risk for COPD as well as those who already have the disease, should be offered at least a brief tobacco dependence counseling at every health care provider visit. **(Grade A, Level 1++)** **Pharmacotherapy** **D** - Pharmacotherapy for smoking cessation is recommended when counseling is not sufficient to help patients quit smoking. **(Grade D, Level 4)** **A** - Treatment of nicotine dependence is effective and should be offered to smokers in addition to counselling. **(Grade A, Level 1++)** In Singapore, there are four types of pharmacotherapies for tobacco dependence available currently, i.e., bupropion SR, nicotine gum, nicotine inhaler, and nicotine patch. **A** - These pharmacotherapies reliably increase long-term smoking abstinence rates and at least one of these medications should be added to counseling if necessary and in the absence of contraindications. **(Grade A, Level 1++)**
Patient Education	
ACP (2007)	No recommendations offered. **Key Points in the Evidence Review for Disease Management and Patient Education** The evidence did not show any effect of disease management programs or patient education on deaths, COPD exacerbations, reduction in all-cause readmissions, hospital length of stay, visits to primary care physicians, clinically meaningful improvement in the St. George Respiratory Questionnaire health status score, patient satisfaction, self management skills, or adherence to treatment.
GOLD (2008)	**Key Points**: • For patients with COPD, health education plays an important role in smoking cessation **(Evidence A)** and can also play a role in improving skills, ability to cope with illness and health status. Studies that have been done indicate that patient education alone does not improve exercise performance or lung function **(Evidence B)**, but it can play a role in improving skills, ability to cope with

	illness, and health status. These outcomes are not traditionally measured in clinical trials, but they may be most important in COPD where even pharmacologic interventions generally confer only a small benefit in terms of lung function. Patient education regarding smoking cessation has the greatest capacity to influence the natural history of COPD. Evaluation of the smoking cessation component in a long-term, multicenter study indicates that if effective resources and time are dedicated to smoking cessation, 25% long-term quit rates can be maintained **(Evidence A)**. Education also improves patient response to exacerbations **(Evidence B)**. Prospective end-of-life discussions can lead to understanding of advance directives and effective therapeutic decisions at the end of life **(Evidence B)**. Ideally, educational messages should be incorporated into all aspects of care for COPD and may take place in many settings: consultations with physicians or other health care workers, home-care or outreach programs, and comprehensive pulmonary rehabilitation programs. **Components of an Education Program** The topics that seem most appropriate for an education program include: smoking cessation; basic information about COPD and pathophysiology of the disease; general approach to therapy and specific aspects of medical treatment; self-management skills; strategies to help minimize dyspnea; advice about when to seek help; self-management and decision-making during exacerbations; and advance directives and end-of-life issues (see Figure 5.3-2 in the original guideline document). Education should be part of consultations with health care workers beginning at the time of first assessment for COPD and continuing with each follow-up visit. The intensity and content of these educational messages should vary depending on the severity of the patient's disease. In practice, a patient often poses a series of questions to the physician (Figure 5.3-3 in the original guideline document). It is important to answer these questions fully and clearly, as this may help make treatment more effective.
SMOH (2006)	**Patient Education** **D** - Patient education is a vital part of COPD management and should begin at the time of first assessment for COPD and continue with each follow-up visit. **(Grade D, Level 4)** **D** - The intensity and content of patient educational messages should vary depending on the severity of the patient's disease (see Table 8 in the original guideline document).

	D - Patient education should be: • Tailored to meet the needs of the individual patient • Interactive • Directed to improving quality of life • Simple to follow • Practical • Appropriate to the intellectual and social skill of the patient and the caregivers **(Grade D, Level 4)** **End of Life Care in COPD** **D** - Patients should be educated about their disease, prognosis and possible circumstances of death. **(Grade D, Level 3)** **D** - Physicians should discuss end of life issues and advance care planning with patients (and their relatives) who have severe to very severe COPD. **(Grade D, Level 3)** **B** - Physicians who look after severe to very severe COPD patients (as with all physicians caring for the terminally ill) will need to be prepared to discuss end of life issues with patients. **(Grade B, Level 1+)**
Surgery	
ACP (2007)	No recommendations offered.
GOLD (2008)	*Bullectomy*. Bullectomy is an older surgical procedure for bullous emphysema. Removal of a large bulla that does not contribute to gas exchange decompresses the adjacent lung parenchyma. Bullectomy can be performed thoracoscopically. In carefully selected patients, this procedure is effective in reducing dyspnea and improving lung function **(Evidence C)**. *LVRS*. Although the results of a large multicenter study showed some very positive results of surgery in a select group of patients, LVRS is an expensive palliative surgical procedure and can be recommended only in carefully selected patients. *Lung transplantation*. In appropriately selected patients with very advanced COPD, lung transplantation has been shown to improve quality of life and functional capacity **(Evidence C)**, although the Joint United Network for Organ Sharing in 1998 found that lung transplantation does not confer a survival benefit in patients with endstage emphysema after two years. Criteria for referral for lung transplantation include FEV_1 < 35% predicted, PaO_2 < 7.3 to 8.0 kPa

	(55 to 60 mm Hg), $PaCO_2$ > 6.7 kPa (50 mm Hg), and secondary pulmonary hypertension. **Note**: Refer to the original guideline document for a discussion of postoperative pulmonary complications.
SMOH (2006)	**Surgical Options for COPD Patients** There are a variety of surgical options available for patients with COPD. These options are primarily focused at improving symptoms and restoring function in a select group of COPD patients. The surgical options available are: 1. Bullectomy 2. Lung volume reduction surgery 3. Lung transplantation **Bullectomy** Surgical removal of large bullae in COPD patients may improve symptoms, exercise tolerance and pulmonary function. **D** - Selection of patients with giant bullae who will benefit from bullectomy should be based on clinical, radiological and pulmonary physiological parameters as indicated below (refer to the original guideline document for parameters). **(Grade D, Level 3)** **LVRS** Overall LVRS has been shown to improve FEV_1, exercise tolerance, quality of life and may be long-term survival. The effect of LVRS seems to be maximal at 6 months post surgery. **A** - Selection of patients that will benefit from LVRS is based on the following indications and contraindications (refer to the original guideline document). **(Grade A, Level 1+)** Investigations for patients being considered for LVRS include the following: 1. High resolution computed tomography thorax 2. Pulmonary Function Test including Diffusion Capacity 3. Arterial Blood gas 4. Cycle ergometry to determine exercise capacity post-pulmonary rehabilitation 5. 2D-echocardiogram or right heart catheter study to determine pulmonary arterial pressure

GPP - LVRS and lung transplantation are surgical options, which are usually considered in selected patients with advanced COPD unresponsive to medical therapy. These patients should be referred to specialty centres where these procedures are done for further evaluation.

Lung Transplantation

COPD is the most common indication for lung transplantation.

The choice of bilateral lung transplantation (BLT) or single lung transplantation (SLT) for COPD remains controversial. Bilateral lung transplantation results in greater improvement in FEV_1, but improvements in exercise capacity are not always significantly greater than SLT.

Lung transplantation leads to improvement in FEV_1, exercise capacity and quality of life.

D - Lung transplantation should be considered in selected patients with end-stage COPD. Refer to the original guideline document for selection criteria. **(Grade D, Level 3 & 4)**

Compared to patients with other cardiopulmonary disease, patients with COPD exhibit the best overall survival after lung transplantation.

Surgery in COPD Patients

GPP - Preoperative assessment of a COPD patient should include:

1. Detailed history and physical examination
2. Assessment of functional capacity (American Society of Anesthesiology Physical Status Scale). See Table 10 in the original guideline document.
3. Preoperative Spirometry
4. Arterial Blood Gas especially in moderate to severe COPD
5. Chest Radiograph

(GPP)

A - COPD patients being considered for surgery should be assessed for risk of developing venous thromboembolism and also for thromboprophylaxis during the perioperative assessment. **(Grade A, Level 1+)**

A - Combination of bronchodilators, chest physiotherapy, antibiotics, smoking cessation for at least 4 to 8 weeks and a short course of oral corticosteroids should be given for patients with acute exacerbation so as to reduce the risk of postoperative pulmonary

	complications. **(Grade A Level 1+)** COPD patients who have symptoms and signs of airflow obstruction should be treated aggressively. Elective surgery in these patients should be deferred, especially if the patient has an acute exacerbation.
ONGOING ASSESSMENT AND FOLLOW-UP **Abbreviations** **Back to TOC**	
ACP (2007)	No recommendations offered.
GOLD (2008)	**Ongoing Monitoring and Assessment** Visits to health care facilities will increase in frequency as COPD progresses. The type of health care workers seen, and the frequency of visits, will depend on the health care system. Ongoing monitoring and assessment in COPD ensures that the goals of treatment are being met and should include evaluation of: (1) exposure to risk factors, especially tobacco smoke; (2) disease progression and development of complications; (3) pharmacotherapy and other medical treatment; (4) exacerbation history; (5) comorbidities. Suggested questions for follow-up visits are listed in Figure 5.1-8 of the original guideline document. The best way to detect changes in symptoms and overall health status is to ask the patient the same questions at each visit. **Monitor Disease Progression and Development of Complications** COPD is usually a progressive disease. Lung function can be expected to worsen over time, even with the best available care. Symptoms and objective measures of airflow limitation should be monitored to determine when to modify therapy and to identify any complications that may develop. As at the initial assessment, follow-up visits should include a physical examination and discussion of symptoms, particularly any new or worsening symptoms. *Pulmonary function*. A patient's decline in lung function is best tracked by periodic spirometry measurements although useful information about lung function decline is unlikely from spirometry measurements performed more than once a year. Spirometry should be performed if there is a substantial increase in symptoms or a complication. Other pulmonary function tests, such as flow-volume loops, diffusing capacity (DLCO) measurements, inspiratory capacity, and measurement of lung volumes are not needed in a routine assessment but can provide information about the overall impact of the disease and can be valuable in resolving diagnostic uncertainties

and assessing patients for surgery.

Arterial blood gas measurement. The development of respiratory failure is indicated by a PaO_2 < 8.0 kPa (60 mm Hg) with or without $PaCO_2$ > 6.7 kPa (50 mm Hg) in arterial blood gas measurements made while breathing air at sea level. Screening patients by pulse oximetry and assessing arterial blood gases in those with an oxygen saturation (SaO_2) < 92% is a useful way of selecting patients for arterial blood gas measurement. However, pulse oximetry gives no information about CO_2 tensions. Clinical signs of respiratory failure or right heart failure include central cyanosis, ankle swelling, and an increase in the jugular venous pressure. Clinical signs of hypercapnia are extremely nonspecific outside of exacerbations.

Assessment of pulmonary hemodynamics. Mild to moderate pulmonary hypertension (mean pulmonary artery pressure > 30 mm Hg) is only likely to be important in patients who have developed respiratory failure. Measurement of pulmonary arterial pressure is not recommended in clinical practice as it does not add practical information beyond that obtained from a knowledge of PaO_2.

Diagnosis of right heart failure or cor pulmonale. Elevation of the jugular venous pressure and the presence of pitting ankle edema are often the most useful findings suggestive of cor pulmonale in clinical practice. However, the jugular venous pressure is often difficult to assess in patients with COPD, due to large swings in intrathoracic pressure. Firm diagnosis of cor pulmonale can be made through a number of investigations, including radiography, electrocardiography, echocardiography, radionucleotide scintigraphy, and magnetic resonance imaging. However, all of these measures involve inherent inaccuracies of diagnosis.

CT and ventilation-perfusion scanning. Despite the benefits of being able to delineate pathological anatomy, routine CT and ventilation-perfusion scanning are currently confined to the assessment of COPD patients for surgery. HRCT is currently under investigation as a way of visualizing airway and parenchymal pathology more precisely.

Hematocrit. Polycythemia can develop in the presence of arterial hypoxemia, especially in continuing smokers, and can be identified by hematocrit > 55%. Anemia is more prevalent than previously thought, affecting almost a quarter of COPD patients in one hospital series. A low hematocrit indicates a poor prognosis in COPD patients receiving long-term oxygen treatment.

Respiratory muscle function. Respiratory muscle function is usually measured by recording the maximum inspiratory and expiratory mouth pressures. More complex measurements are confined to research laboratories. Measurement of inspiratory muscle force is useful in assessing patients when dyspnea or hypercapnia is not readily explained by lung function testing or when peripheral muscle

weakness is suspected. This measurement may improve in COPD patients when other measurements of lung mechanics do not (e.g., after pulmonary rehabilitation).

Sleep studies. Sleep studies may be indicated when hypoxemia or right heart failure develops in the presence of relatively mild airflow limitation or when the patient has symptoms suggesting the presence of sleep apnea.

Exercise testing. Several types of tests are available to measure exercise capacity (e.g., treadmill and cycle ergometry in the laboratory — or six-minute and shuttle walking tests), but these are primarily used in conjunction with pulmonary rehabilitation programs.

Monitor Pharmacotherapy and Other Medical Treatment

In order to adjust therapy appropriately as the disease progresses, each follow-up visit should include a discussion of the current therapeutic regimen. Dosages of various medications, adherence to the regimen, inhaler technique, effectiveness of the current regime at controlling symptoms, and side effects of treatment should be monitored.

Monitor Exacerbation History

During periodic assessments, health care workers should question the patient and evaluate any records of exacerbations, both self-treated and those treated by other health care providers. Frequency, severity, likely causes of exacerbations, and the patient's psychological well-being should be evaluated. Increased sputum volume, acutely worsening dyspnea, and the presence of purulent sputum should be noted. Specific inquiry into unscheduled visits to providers, telephone calls for assistance, and use of urgent or emergency care facilities may be helpful. Severity can be estimated by the increased need for bronchodilator medication or glucocorticosteroids and by the need for antibiotic treatment. Hospitalizations should be documented, including the facility, duration of stay, and any use of critical care or intubation. The clinician then can request summaries of all care received to facilitate continuity of care.

Monitor Comorbidities

Comorbidities are common in COPD. Some may be an indirect result of COPD, arising independently but more likely to occur when COPD is present, e.g., ischemic heart disease, bronchial carcinoma, osteoporosis, and depression. Other comorbid conditions may coexist with COPD because they become prevalent as part of the aging process, e.g., arthritis, diabetes, reflux esophagitis. All comorbid

	conditions become harder to manage when COPD is present, either because COPD adds to the total level of disability or because COPD therapy adversely affects the comorbid disorder. All comorbid conditions amplify the disability associated with COPD and can potentially complicate its management. Until more integrated guidance about disease management for specific comorbid problems becomes available, the focus should be on identification and management of these individual problems in line with local treatment guidance.
SMOH (2006)	**Monitoring of Patients with Stable COPD** **D & GPP** - Patients should be seen and assessed regularly (e.g., three monthly in the stable state). At each follow-up visit: • Patients should be asked regarding onset of any new symptoms and/or worsening of exercise capacity. • Current smokers should be given repeated advice to quit. • Adherence to medications should be assessed, and the patient's inhaler technique checked and re-taught if necessary. **(Grade D, Level 4/GPP)** **D & GPP** - Indications for specialist referral: • Severe COPD (FEV_1 < 50% predicted) • Frequent exacerbations (e.g., two or more a year) despite compliance to treatment • Rapidly progressive course of the disease • Development of new symptoms (e.g., haemoptysis) or new physical signs (e.g., cyanosis, peripheral oedema) **(Grade D, Level 4/GPP)**

STRENGTH OF EVIDENCE AND RECOMMENDATION GRADING SCHEMES **Abbreviations** **Back to TOC**	
ACP (2007)	**Table: American College of Physicians Guideline Grading System***

Quality of Evidence	Strength of Recommendation	
	Benefits clearly outweigh risks and	Benefits finely

	burden OR risks and burden clearly outweigh benefits	balanced with risks and burden
High	Strong	Weak
Moderate	Strong	Weak
Low	Strong	Weak
Insufficient evidence to determine net benefits or harms		

* Adopted from the classification developed by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) workgroup.

GOLD (2008)

Levels of Evidence

A. Randomized controlled trials (RCTs). Rich body of data.
Definition: Evidence is from endpoints of well-designed RCTs that provide a consistent pattern of findings in the population for which the recommendation is made. Category A requires substantial numbers of studies involving substantial numbers of participants.

B. Randomized controlled trials. Limited body of data.
Definition: Evidence is from endpoints of intervention studies that include only a limited number of patients, posthoc or subgroup analysis of RCTs, or meta-analysis of RCTs. In general, Category B pertains when few randomized trials exist, they are small in size, they were undertaken in a population that differs from the target population of the recommendation, or the results are somewhat inconsistent.

C. Nonrandomized trials. Observational studies.
Definition: Evidence is from outcomes of uncontrolled or nonrandomized trials or from observational studies.

D. Panel consensus. Judgment.
Definition: This category is used only in cases where the provision of some guidance was deemed valuable but the clinical literature addressing the subject was deemed insufficient to justify placement in one of the other categories. The Panel Consensus is based on clinical experience or knowledge that does not meet the above-listed criteria.

SMOH (2006)

Grades of Recommendation

Grade A: At least one meta-analysis, systematic review of randomized controlled trials (RCTs), or RCT rated as 1++ and directly applicable to the target population; or

A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results

Grade B: A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall

	consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+ **Grade C**: A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++ **Grade D**: Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+ **GPP** (good practice points): Recommended best practice based on the clinical experience of the guideline development group. **Levels of Evidence** **Level 1++**: High quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias. **Level 1+**: Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias. **Level 1-**: Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias **Level 2++**: High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal **Level 2+**: Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal **Level 2-**: Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal **Level 3**: Non-analytic studies (e.g. case reports, case series) **Level 4**: Expert opinion

COMPARISON OF METHODOLOGY

Click on the links below for details of guideline development methodology		
ACP (2007)	**GOLD (2008)**	**SMOH (2006)**
All of the guidelines performed searches of electronic database to collect the evidence; ACP and GOLD also performed hand searches of published literature (both searched primary sources, GOLD searched primary and secondary sources). The ACP guideline differs from the others in that is based on a Minnesota Evidence-based Practice Center evidence report sponsored by the Agency for Healthcare Research and Quality. ACP and GOLD provide details regarding the collection/selection of evidence, such as the names of databases searched, date ranges, and search terms. All of the groups used weighting according to a rating scheme to assess the quality and strength of the evidence, and all provide the scheme. To analyze the evidence, all three groups performed a systematic review; the ACP and GOLD systematic reviews incorporated evidence tables. GOLD and SMOH also reviewed published meta-analyses. Only ACP provides a description of the methods used to analyze the evidence. With regard to formulation of recommendations, ACP is explicit about the scientific rationale for its recommendations and uses an informal process to evaluate and formulate the recommendations based on the evidence. Expert consensus was employed by GOLD and SMOH. ACP and SMOH recommendations are graded; both groups provide the rating schemes for the strength of the recommendations. ACP and GOLD provide a description of the processes used to develop the recommendations. Internal and external peer review was utilized by ACP and SMOH to validate their guidelines. SMOH does not specify a method of guideline validation.		

SOURCE(S) OF FUNDING Abbreviations Back to TOC	
ACP (2007)	American College of Physicians (ACP)
GOLD (2008)	Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Dey, GlaxoSmithKline, Mitsubishi Tanabe Pharma, Novartis, Nycomed, Pfizer, Schering-Plough, Sepracor
SMOH (2006)	Singapore Ministry of Health

BENEFITS AND HARMS Abbreviations Back to TOC	
Benefits	
ACP (2007)	Appropriate management of patients with COPD, leading to a reduction in hospitalizations, improved health status and exercise capacity
GOLD (2008)	Appropriate diagnosis, management, and prevention of COPD
SMOH (2006)	Appropriate diagnosis and management of patients with COPD
Harms	
ACP (2007)	Adverse effects associated with treatment
GOLD (2008)	*Arterial Blood Gas Measurement*: Adequate pressure must be applied at the arterial puncture site for at least one minute, as failure to do so can lead to painful bruising. *Beta$_2$-agonists*: Stimulation of beta$_2$-receptors can produce resting sinus tachycardia and has the potential to precipitate cardiac rhythm disturbances in very susceptible patients, although this appears to be a remarkably rare event with inhaled therapy. Exaggerated somatic tremor is troublesome in some older patients treated with higher doses of beta$_2$-agonists, whatever the route of administration, and this limits the dose that can be tolerated. Although hypokalemia can occur, especially when treatment is combined with thiazide diuretics, and oxygen consumption can be increased under resting conditions, these metabolic effects show tachyphylaxis unlike the bronchodilator actions. Mild falls in PaO_2 occur after administration of both short- and long-acting beta$_2$-agonists, but the clinical significance of these changes is doubtful. Despite the concerns raised some years ago, further detailed study has found no association between beta$_2$-agonist use and an accelerated loss of lung function or increased mortality in COPD. *Anticholinergics*: Anticholinergic drugs are poorly absorbed, which limits the troublesome systemic effects seen with atropine. Extensive use of this class of inhaled agents in a wide range of doses and clinical settings has shown them to be very safe. The main side effect is dryness of the mouth. Twenty-one days of inhaled tiotropium, 18 micrograms a day as a dry powder, does not retard mucus clearance from the lungs. Although occasional prostatic symptoms have been reported, there are no data to prove a true causal relationship. A bitter,

	metallic taste is reported by some patients using ipratropium. An unexpected small increase in cardiovascular events in COPD patients regularly treated with ipratropium bromide has been reported and requires further investigation. Use of wet nebulizer solutions with a face mask has been reported to precipitate acute glaucoma, probably by a direct effect of the solution on the eye. Mucociliary clearance is unaffected by theses drugs, and respiratory infection rates are not increased. *Methylxanthines*: Toxicity is dose related, a particular problem with the xanthine derivatives because their therapeutic ratio is small and most of the benefit occurs only when near-toxic doses are given. Methylxanthines are nonspecific inhibitors of all phosphodiesterase enzyme subsets, which explains their wide range of toxic effects. Problems include the development of atrial and ventricular arrhythmias (which can prove fatal) and grand mal convulsions (which can occur irrespective of prior epileptic history). More common and less dramatic side effects include headaches, insomnia, nausea, and heartburn, and these may occur within the therapeutic range of serum theophylline. Unlike the other bronchodilator classes, xanthine derivatives may involve a risk of overdose (either intentional or accidental). *Oral Glucocorticosteroids*: A side effect of long-term treatment with systemic glucocorticosteroids is steroid myopathy, which contributes to muscle weakness, decreased functionality, and respiratory failure in subjects with advanced COPD. *Narcotics (morphine)*: Some clinical studies suggest that morphine used to control dyspnea may have serious adverse effects, and its benefits may be limited to a few sensitive subjects. *Lung Transplantation*: The common complications seen in COPD patients after lung transplantation, apart from operative mortality, are acute rejection and bronchiolitis obliterans, cytomegalovirus (CMV), other opportunistic fungal (Candida, Aspergillus, Cryptococcus, Carinii) or bacterial (Pseudomonas, Staphylococcus species) infections, lymphoproliferative disease, and lymphomas. *Invasive Mechanical Ventilation*: Major hazards include the risk of ventilator-acquired pneumonia (especially when multi-resistant organisms are prevalent), barotrauma, and failure to wean to spontaneous ventilation.
SMOH (2006)	• Side effects of medication • Complications related to surgery • Risk of fire and explosion when using oxygen therapy. Patients requiring oxygen therapy should be advised against smoking cigarettes.

CONTRAINDICATIONS Abbreviations Back to TOC	
ACP (2007)	Not applicable
GOLD (2008)	• Special consideration should be given before using pharmacotherapy for smoking cessation in selected populations: people with medical contraindications, light smokers (fewer than 10 cigarettes/day), and pregnant and adolescent smokers. • **Nicotine Replacement Therapy**: Medical contraindications to nicotine replacement therapy include unstable coronary artery disease, untreated peptic ulcer disease, and recent myocardial infarction or stroke. • **Vasodilators**: In patients with stable chronic obstructive pulmonary disease (COPD), inhaled nitric oxide can worsen gas exchange because of altered hypoxic regulation of ventilation-perfusion balance and thus is contraindicated. • **Beta-Blockers**: Beta-blockers commonly prescribed for heart disease are usually contraindicated in COPD. • **Noninvasive Intermittent Ventilation** Relative Contraindications for Noninvasive Intermittent Ventilation (NIV): • Respiratory arrest • Cardiovascular instability (hypotension, arrhythmias, myocardial infarction) • Change in mental status; uncooperative patient • High aspiration risk • Viscous or copious secretions • Recent facial or gastroesophageal surgery • Craniofacial trauma • Fixed nasopharyngeal abnormalities • Burns • Extreme obesity
SMOH (2006)	Contraindications to specific surgeries (bullectomy, lung volume reduction surgery [LVRS]) and lung transplantation are listed in the original guideline document.

Abbreviations
Back to TOC

AAT, Alpha1-antitrypsin

AO, Airflow obstruction

ACP, American College of Physicians

BMI, Body mass index

CT, Computed tomography

COPD, Chronic obstructive pulmonary disease

ERS, European Respiratory Society

FEV_1, Forced expiratory volume in one second

FVC, Forced vital capacity

GOLD, Global Initiative for Chronic Obstructive Lung Disease

HRCT, High-resolution computed tomography

ICS, Inhaled corticosteroid

LABA, long-acting $beta_2$-agonist

LTOT, Long-term oxygen therapy

LVRS, Lung volume reduction surgery

MRC, Medical Research Council

PEF, Peak expiratory flow

PEP, Positive expiratory pressure

SAAC, Short-acting anti-cholinergic

SABA, Short-acting $beta_2$-agonist

SMOH, Singapore Ministry of Health

TLCO, Transfer factor for carbon monoxide

VC, Vital capacity

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2006 to incorporate the updated FMS guideline. This synthesis was updated on June 4, 2008 to incorporate updated guidelines from GOLD. This synthesis was updated in September 2009 to update GOLD recommendations, to add ACP recommendations, and to remove FMS and NICE recommendations. The information was verified by ACP on September 30, 2009.

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